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CROFTON, 1998 e

MEMORANDUM

Date: 24 September 1998 (revised 06 November 1998)

Subject: Analysis of the Thyroid Hormone Data from the Rat Developmental Neurotoxicology Study

From: Kevin M. Crofton 
Neurotoxicology Division, MD-74B
National Health Effects and Environmental Research Laboratory

To: Annie Jarabek
National Center for Environmental Assessment

Attached is the statistical analysis of the hormone data from the Argus Rat Developmental Neurotoxicology Study (Argus, 1998a; #1613-002). I have attached a description of how the analyses were done and some summary graphs.

NOTE: The raw data analyzed herein was not formally submitted to the Agency at the time of this analysis. Data were supplied in electronic form by Dr. David Mattie, WPAFB.

Analyses of Hormone Data from the Argus Developmental Neurotoxicology Study

Summary: The report from Argus Laboratories (Argus, 1998a) contains thyroid hormone and thyrotrophin data from the Developmental Neurotoxicology Study of ammonium perchlorate in the rat. The following is a statistical analysis of the thyroid and pituitary hormone data (T4, thyroxine; T3, triiodothyronine; TSH, thyroid stimulating hormone) found in that report. At the time of this analysis, data were available from both the F1 generation (male and females samples were pooled for each litter) on postnatal day 5 (PND5) and the F0 generation on PND10. Only the F1 data were re-analyzed due to the very limited ($n=2-5/\text{group}$) data from F0 PND10 group.

Results of these re-analyses are similar to those stated in the Argus (1998a) report. There was a significant decrease in both T3 and T4, as well as the expected increases in TSH. The NOAELs for the effects of perchlorate on T3, T4, and TSH are 0.1, 1.0, and 3.0 mg/kg/day, respectively. These results are consistent with the known mechanism-of-action of perchlorate (inhibition of thyroid hormones). The increased TSH is likely a result of the activation of the pituitary-thyroid feedback mechanism.

Data: All data were supplied in Excel spreadsheets by Dr. David Mattie (note: AFRL/HEST did the analytical work on the samples supplied by Argus). Data were exported as ascii files for analyses by SAS. Data for dependent measures (T4, T3 and TSH) were subjected to separate one-way ANOVAs. Treatment (dose) was as the independent between-subjects variable. Mean contrasts were performed using Tukey's Studentized Range (HSD) Test. To correct for multiple comparisons (i.e., separate analyses for T4 and TSH) the acceptable alpha for significance (for all interaction main effects tests) was corrected to 0.028 (alpha of 0.05 divided by the square root of the number of ANOVAs). SAS analysis code and output are attached in Appendix 1.

Data Analysis - Results: There were significant main effects of Treatment effects for all the hormones. The data are plotted in Figures 1 - 3.

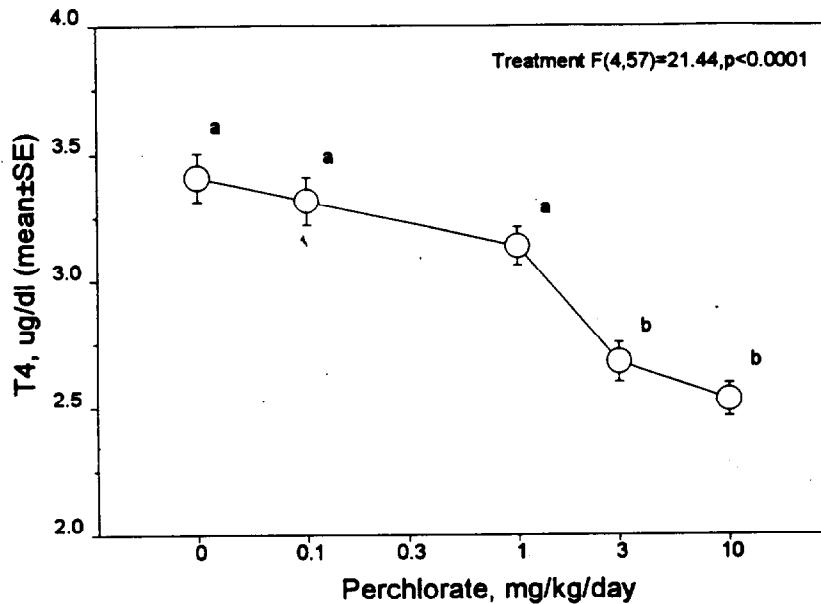


Figure 1. Effects of maternal perchlorate exposure of serum total thyroxine (T4) concentrations in F1 generation offspring on postnatal day 5. Means with different letters were significantly different ($p<0.05$). Daily dose was estimated from water consumption data.

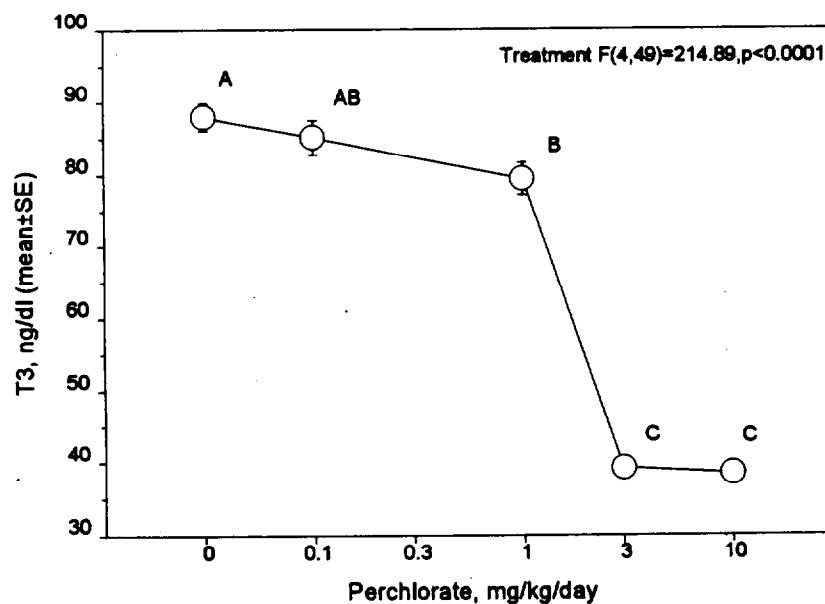


Figure 2. Effects of maternal perchlorate exposure of serum total triiodothyronine (T3) concentrations in F1 generation offspring on postnatal day 5. Means with different letters were significantly different ($p<0.05$). Daily dose was estimated from water consumption data.

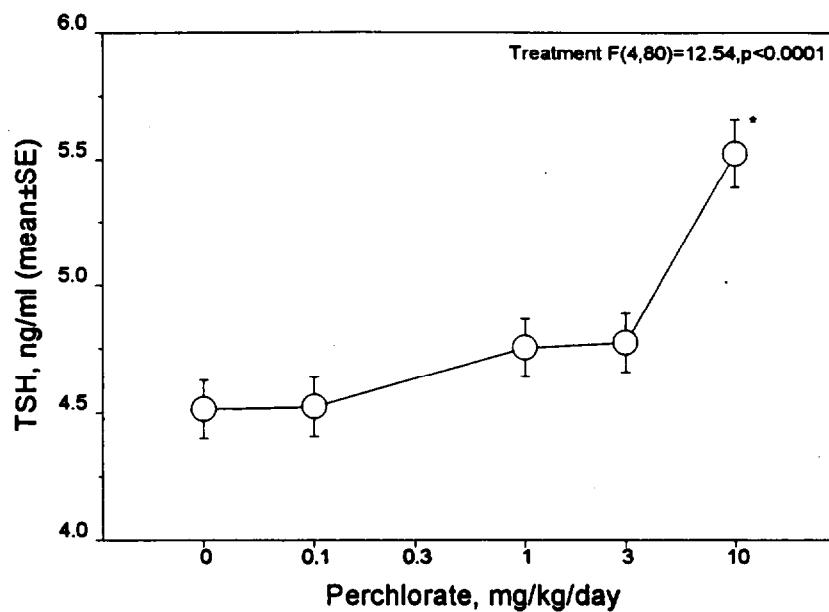


Figure 3. Effects of maternal perchlorate exposure of serum thyroid stimulation hormone (TSH) concentrations in F1 generation offspring on postnatal day 5. *= significantly different from control group, $p<0.05$.

APPENDIX 1 - SAS ANALYSIS FOR HORMONE DATA

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The SAS System

14:03

NOTE: Copyright (c) 1989-1996 by SAS Institute Inc., Cary, NC, USA.
 NOTE: SAS (r) Proprietary Software Release 6.12 TS020
 Licensed to US ENVIRONMENTAL PROTECTION AGENCY, Site 0019614059.

NOTE: Running on ALPHASERVER Model 2100 5/300 Serial Number 80000000.

Welcome to the NHEERL-RTP SAS Information Delivery System.

```

1      *THIS FILE IS FOUND AT [Crofton.THYROID.perchlorate]perchlorate_dn_pnd5.SAS;
2      *IT ANALYZES THE THYROID HORMONE DATA FROM THE WPAFB 90 DAY PERCHLORATE STUDY;
3
4
5      *INPUT DATA INTO SAS DATASET;
6      DATA RAW; INFILE '[CROFTON.THYROID.PERCHLORATE]PERCHLORATE_DN_PND5.Txt';
7          INPUT WPAFB $ 1-16 DOSE $ ANIM TSH T4 T3;
8
9      *ASSIGN DOSAGE VALUES TO TREATMENT CODES;
10     IF DOSE = '1' THEN TRT = '1-----CONTROL';
11     IF DOSE = '2' THEN TRT = '2--0.1_mg/kg/day';
12     IF DOSE = '3' THEN TRT = '3--1.0_mg/kg/day';
13     IF DOSE = '4' THEN TRT = '4--3.0_mg/kg/day';
14     IF DOSE = '5' THEN TRT = '5-10.0_mg/kg/day';
15

```

NOTE: The infile '[CROFTON.THYROID.PERCHLORATE]PERCHLORATE_DN_PND5.Txt' is:
 File=DSA21:[SAS\$USERS.CROFTON.THYROID.PERCHLORATE]PERCHLORATE_DN_PND5.TXT

NOTE: 85 records were read from the infile '[CROFTON.THYROID.PERCHLORATE]PERCHLORATE_DN_PND5.Txt'.
 The minimum record length was 43.
 The maximum record length was 45.

NOTE: The data set WORK.RAW has 85 observations and 7 variables.

```

16      PROC PRINT;
17
18      *SORT DATA BY TRT -- THEN GET MEANS;
19
20

```

NOTE: The PROCEDURE PRINT printed pages 1-2.

```

20      PROC SORT; BY TRT;

```

21

NOTE: The data set WORK.RAW has 85 observations and 7 variables.

21 PROC MEANS N MEAN STDERR MIN MAX STD VAR CV; BY TRT;
22 VAR TSH T3 T4;

23

24
25 *RUN ONE WAY ANOVAs FOR ALL VARIABLES;
26

NOTE: The PROCEDURE MEANS printed page 3.

26 PROC SORT; BY TRT;

27

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NOTE: Input data set is already sorted, no sorting done.

27 PROC GLM;
28 CLASSES TRT;
29 MODEL TSH T3 T4 = TRT;
30 MEANS TRT/TUKEY LINES;
31 TITLE1 "ARGUS DEVELOPMENTAL NEURO PND5 PUP THYROID HORMONES - ALL VARIABLES";
32 TITLE2 "PROC GLM - MAIN EFFECT OF TRT - WITH TUKEYS";
33 ENDSAS;

NOTE: The PROCEDURE GLM printed pages 4-10.

NOTE: SAS Institute Inc., SAS Campus Drive, Cary, NC USA 27513-2414

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OBS	WPAFB	DOSE	ANIM	TSH	T4	T3	TRT
1	1,F1/MandF,19508	1	19508	4.15	3.17	.	1-----CONTROL
2	1,F1/MandF,19520	1	19520	4.23	2.67	88.8	1-----CONTROL
3	1,F1/MandF,19523	1	19523	4.36	3.49	91.1	1-----CONTROL
4	1,F1/MandF,19526	1	19526	4.06	.	97.9	1-----CONTROL
5	1,F1/MandF,19530	1	19530	4.12	3.37	84.0	1-----CONTROL
6	1,F1/MandF,19549	1	19549	4.68	3.67	82.1	1-----CONTROL
7	1,F1/MandF,19556	1	19556	4.19	3.83	84.1	1-----CONTROL
8	1,F1/MandF,19558	1	19558	4.94	3.29	86.0	1-----CONTROL
9	1,F1/MandF,19571	1	19571	4.09	.	86.5	1-----CONTROL
10	1,F1/MandF,19580	1	19580	4.15	3.07	.	1-----CONTROL
11	1,F1/MandF,19582	1	19582	4.30	2.90	.	1-----CONTROL
12	1,F1/MandF,19585	1	19585	4.72	3.52	.	1-----CONTROL
13	1,F1/MandF,19608	1	19608	4.34	3.81	.	1-----CONTROL
14	1,F1/MandF,19610	1	19610	4.94	3.85	.	1-----CONTROL
15	1,F1/MandF,19611	1	19611	5.46	3.54	.	1-----CONTROL
16	1,F1/MandF,19614	1	19614	5.53	3.85	81.5	1-----CONTROL
17	1,F1/MandF,19621	1	19621	4.45	3.11	97.7	1-----CONTROL
18	2,F1/MandF,19511	2	19511	4.60	3.37	94.1	2--0.1_mg/kg/day
19	2,F1/MandF,19514	2	19514	3.87	3.04	.	2--0.1_mg/kg/day
20	2,F1/MandF,19527	2	19527	5.01	3.67	77.8	2--0.1_mg/kg/day
21	2,F1/MandF,19533	2	19533	3.88	2.87	79.5	2--0.1_mg/kg/day
22	2,F1/MandF,19534	2	19534	4.19	3.43	92.3	2--0.1_mg/kg/day
23	2,F1/MandF,19536	2	19536	4.62	.	.	2--0.1_mg/kg/day
24	2,F1/MandF,19542	2	19542	4.94	3.30	77.9	2--0.1_mg/kg/day
25	2,F1/MandF,19575	2	19575	4.20	3.23	90.9	2--0.1_mg/kg/day
26	2,F1/MandF,19576	2	19576	4.09	3.05	83.3	2--0.1_mg/kg/day
27	2,F1/MandF,19590	2	19590	4.30	3.84	74.5	2--0.1_mg/kg/day
28	2,F1/MandF,19593	2	19593	4.76	3.03	94.9	2--0.1_mg/kg/day
29	2,F1/MandF,19594	2	19594	4.89	.	.	2--0.1_mg/kg/day
30	2,F1/MandF,19605	2	19605	5.25	3.67	86.1	2--0.1_mg/kg/day
31	2,F1/MandF,19662	2	19662	4.71	.	.	2--0.1_mg/kg/day
32	3,F1/MandF,19504	3	19504	4.56	3.69	74.3	3--1.0_mg/kg/day
33	3,F1/MandF,19521	3	19521	4.74	3.50	89.5	3--1.0_mg/kg/day
34	3,F1/MandF,19535	3	19535	4.04	2.92	91.3	3--1.0_mg/kg/day
35	3,F1/MandF,19538	3	19538	5.13	2.91	75.5	3--1.0_mg/kg/day
36	3,F1/MandF,19539	3	19539	4.40	3.15	80.9	3--1.0_mg/kg/day
37	3,F1/MandF,19547	3	19547	4.51	3.11	78.1	3--1.0_mg/kg/day
38	3,F1/MandF,19568	3	19568	4.39	3.31	.	3--1.0_mg/kg/day
39	3,F1/MandF,19579	3	19579	4.38	.	.	3--1.0_mg/kg/day
40	3,F1/MandF,19584	3	19584	4.89	2.71	70.8	3--1.0_mg/kg/day
41	3,F1/MandF,19586	3	19586	4.22	.	.	3--1.0_mg/kg/day

42	3,F1/MandF,19587	3	19587	5.61	2.98	78.9	3--1.0_mg/kg/day
43	3,F1/MandF,19588	3	19588	4.98	.	.	3--1.0_mg/kg/day
44	3,F1/MandF,19589	3	19589	5.63	.	.	3--1.0_mg/kg/day
45	3,F1/MandF,19592	3	19592	4.78	3.18	71.0	3--1.0_mg/kg/day
46	3,F1/MandF,19596	3	19596	5.28	2.84	83.5	3--1.0_mg/kg/day
47	3,F1/MandF,19597	3	19597	4.03	.	.	3--1.0_mg/kg/day
48	3,F1/MandF,19603	3	19603	4.88	3.33	.	3--1.0_mg/kg/day
49	3,F1/MandF,19616	3	19616	5.11	3.15	.	3--1.0_mg/kg/day
50	4,F1/MandF,19522	4	19522	4.73	2.46	40.4	4--3.0_mg/kg/day
51	4,F1/MandF,19525	4	19525	5.01	2.28	38.9	4--3.0_mg/kg/day
52	4,F1/MandF,19537	4	19537	4.13	2.92	38.0	4--3.0_mg/kg/day
53	4,F1/MandF,19544	4	19544	5.58	2.73	46.1	4--3.0_mg/kg/day
54	4,F1/MandF,19554	4	19554	3.76	2.37	37.2	4--3.0_mg/kg/day
55	4,F1/MandF,19557	4	19557	5.03	2.52	42.4	4--3.0_mg/kg/day
56	4,F1/MandF,19569	4	19569	4.99	3.12	40.0	4--3.0_mg/kg/day

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OBS	WPAFB	DOSE	ANIM	TSH	T4	T3	TRT
57	4,F1/MandF,19573	4	19573	3.97	.	.	4--3.0_mg/kg/day
58	4,F1/MandF,19577	4	19577	4.92	2.78	37.3	4--3.0_mg/kg/day
59	4,F1/MandF,19598	4	19598	4.60	2.76	34.5	4--3.0_mg/kg/day
60	4,F1/MandF,19600	4	19600	5.29	2.90	35.1	4--3.0_mg/kg/day
61	4,F1/MandF,19604	4	19604	4.95	.	43.4	4--3.0_mg/kg/day
62	4,F1/MandF,19607	4	19607	4.92	.	.	4--3.0_mg/kg/day
63	4,F1/MandF,19612	4	19612	4.95	.	.	4--3.0_mg/kg/day
64	4,F1/MandF,19617	4	19617	5.10	2.64	36.7	4--3.0_mg/kg/day
65	4,F1/MandF,19618	4	19618	4.89	.	.	4--3.0_mg/kg/day
66	4,F1/MandF,19622	4	19622	4.34	.	.	4--3.0_mg/kg/day
67	5,F1/MandF,19502	5	19502	4.85	2.17	35.3	5-10.0_mg/kg/day
68	5,F1/MandF,19512	5	19512	5.83	2.52	35.4	5-10.0_mg/kg/day
69	5,F1/MandF,19528	5	19528	5.00	.	.	5-10.0_mg/kg/day
70	5,F1/MandF,19529	5	19529	5.87	2.28	36.6	5-10.0_mg/kg/day
71	5,F1/MandF,19532	5	19532	6.19	2.25	33.7	5-10.0_mg/kg/day
72	5,F1/MandF,19541	5	19541	6.09	2.83	39.3	5-10.0_mg/kg/day
73	5,F1/MandF,19543	5	19543	6.32	.	34.8	5-10.0_mg/kg/day
74	5,F1/MandF,19551	5	19551	6.26	2.68	45.9	5-10.0_mg/kg/day
75	5,F1/MandF,19552	5	19552	4.53	2.73	38.0	5-10.0_mg/kg/day
76	5,F1/MandF,19553	5	19553	5.30	2.78	39.6	5-10.0_mg/kg/day
77	5,F1/MandF,19560	5	19560	5.71	2.51	43.8	5-10.0_mg/kg/day
78	5,F1/MandF,19570	5	19570	4.74	.	.	5-10.0_mg/kg/day
79	5,F1/MandF,19572	5	19572	4.61	2.73	.	5-10.0_mg/kg/day
80	5,F1/MandF,19574	5	19574	5.86	2.58	37.5	5-10.0_mg/kg/day

81	5,F1/MandF,19591	5	19591	5.89	.	.	10.0_mg/kg/day
82	5,F1/MandF,19595	5	19595	5.79	.	.	5-10.0_mg/kg/day
83	5,F1/MandF,19601	5	19601	5.25	2.32	41.6	5-10.0_mg/kg/day
84	5,F1/MandF,19613	5	19613	5.04	.	.	5-10.0_mg/kg/day
85	5,F1/MandF,19620	5	19620	5.79	.	.	5-10.0_mg/kg/day

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----- TRT=1 ----- CONTROL

CV	Variable	N	Mean	Std Error	Minimum	Maximum	Std Dev	Variance
10.2992437	TSH	17	4.5123529	0.1127156	4.0600000	5.5300000	0.4647382	0.2159816
6.7449471	T3	10	87.9700000	1.8763469	81.5000000	97.9000000	5.9335300	35.2067778
10.8437624	T4	15	3.4093333	0.0954561	2.6700000	3.8500000	0.3697000	0.1366781

----- TRT=2 -- 0.1_mg/kg/day

CV	Variable	N	Mean	Std Error	Minimum	Maximum	Std Dev	Variance
9.6449336	TSH	14	4.5221429	0.1165680	3.8700000	5.2500000	0.4361577	0.1902335
8.8910487	T3	10	85.1300000	2.3935121	74.5000000	94.9000000	7.5689497	57.2890000
9.4168493	T4	11	3.3181818	0.0942127	2.8700000	3.8400000	0.3124682	0.0976364

----- TRT=3 -- 1.0_mg/kg/day

CV	Variable	N	Mean	Std Error	Minimum	Maximum	Std Dev	Variance
----	----------	---	------	-----------	---------	---------	---------	----------

10.1347206	TSH	18	4.7533333	0.1135465	4.0300000	5.6300000	0.4817371	0.2320706
8.9113936	T3	10	79.3800000	2.2369523	70.8000000	91.3000000	7.0738643	50.0395556
8.7374120	T4	13	3.1369231	0.0760177	2.7100000	3.6900000	0.2740859	0.0751231

----- TRT=4 - 3.0_mg/kg/day

CV	Variable	N	Mean	Std Error	Minimum	Maximum	Std Dev	Variance
9.9605170	TSH	17	4.7741176	0.1153322	3.7600000	5.5800000	0.4755268	0.2261257
8.8393763	T3	12	39.1666667	0.9994190	34.5000000	46.1000000	3.4620891	11.9860606
9.5145595	T4	11	2.6800000	0.0768824	2.2800000	3.1200000	0.2549902	0.0650200

----- TRT=5 - 10.0_mg/kg/day

CV	Variable	N	Mean	Std Error	Minimum	Maximum	Std Dev	Variance
10.5436789	TSH	19	5.5221053	0.1335734	4.5300000	6.3200000	0.5822330	0.3389953
9.7835885	T3	12	38.4583333	1.0861705	33.7000000	45.9000000	3.7626051	14.1571970
9.0117714	T4	12	2.5316667	0.0658607	2.1700000	2.8300000	0.2281480	0.0520515

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ARGUS DEVELOPMENTAL NEURO PND5 PUP THYROID HORMONES - ALL VARIABLES

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PROC GLM - MAIN EFFECT OF TRT - WITH TUKEYS

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General Linear Models Procedure
Class Level Information

Class	Levels	Values
TRT	5	1-----CONTROL 2--0.1_mg/kg/day 3--1.0_mg/kg/day 4--3.0_mg/kg/day 5-10.0_mg/kg/day

Number of observations in data set = 85

Group	Obs	Dependent Variables
1	85	TSH
2	54	T3
3	62	T4

NOTE: Variables in each group are consistent with respect to the presence or absence of missing values.

1 ARGUS DEVELOPMENTAL NEURO PND5 PUP THYROID HORMONES - ALL VARIABLES
 5 PROC GLM - MAIN EFFECT OF TRT - WITH TUKEYS 14:03
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General Linear Models Procedure

Dependent Variable: TSH

Pr > F	Source	DF	Sum of Squares	Mean Square	F Value
0.0001	Model	4	12.28773556	3.07193389	12.54
	Error	80	19.59386915	0.24492336	
	Corrected Total	84	31.88160471		
TSI Mean		R-Square	C.V.	Root MSE	
4.84305882		0.385418	10.21869	0.49489733	

Pr > F	Source	DF	Type I SS	Mean Square	F Value
0.0001	TRT	4	12.28773556	3.07193389	12.54
Pr > F	Source	DF	Type III SS	Mean Square	F Value
0.0001	TRT	4	12.28773556	3.07193389	12.54

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ARGUS DEVELOPMENTAL NEURO PNDS PUP THYROID HORMONES - ALL VARIABLES

PROC GLM - MAIN EFFECT OF TRT - WITH TUKEYS

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General Linear Models Procedure

Tukey's Studentized Range (HSD) Test for variable: TSH

has a higher type

NOTE: This test controls the type I experimentwise error rate, but generally
 II error rate than REGWQ.

Alpha= 0.05 df= 80 MSE= 0.244923
 Critical Value of Studentized Range= 3.947
 Minimum Significant Difference= 0.4763
 WARNING: Cell sizes are not equal.
 Harmonic Mean of cell sizes= 16.82014

Means with the same letter are not significantly different.

Tukey Grouping	Mean	N	TRT
A	5.5221	19	5-10.0_mg/kg/day
B	4.7741	17	4--3.0_mg/kg/day
B	4.7533	18	3--1.0_mg/kg/day
B	4.5221	14	2--0.1_mg/kg/day
B	4.5124	17	1-----CONTROL

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ARGUS DEVELOPMENTAL NEURO PNDS PUP THYROID HORMONES - ALL VARIABLES

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PROC GLM - MAIN EFFECT OF TRT - WITH TUKEYS

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General Linear Models Procedure

Dependent Variable: T3

Pr > F	Source	DF	Sum of Squares	Mean Square	F Value
0.0001	Model	4	27804.67450000	6951.16862500	216.89
	Error	49	1570.39383333	32.04885374	
	Corrected Total	53	29375.06833333		
T3 Mean	R-Square		C.V.	Root MSE	
64.00555556	0.946540		8.844811	5.66117070	

Pr > F	Source	DF	Type I SS	Mean Square	F Value
0.0001	TRT	4	27804.67450000	6951.16862500	216.89

Pr > F	Source	DF	Type III SS	Mean Square	F Value
0.0001	TRT	4	27804.67450000	6951.16862500	216.89

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ARGUS DEVELOPMENTAL NEURO PNDS PUP THYROID HORMONES - ALL VARIABLES

PROC GLM - MAIN EFFECT OF TRT - WITH TUKEYS

14:03

Tuesday, September 22, 1998

General Linear Models Procedure

Tukey's Studentized Range (HSD) Test for variable: T3

has a higher type

NOTE: This test controls the type I experimentwise error rate, but generally
 II error rate than REGWQ.

Alpha= 0.05 df= 49 MSE= 32.04885
 Critical Value of Studentized Range= 4.005
 Minimum Significant Difference= 6.9267
 WARNING: Cell sizes are not equal.
 Harmonic Mean of cell sizes= 10.71429

Means with the same letter are not significantly different.

Tukey Grouping		Mean	N	TRT
	A	87.970	10	1-----CONTROL
	A	85.130	10	2--0.1_mg/kg/day
B	A	85.130	10	2--0.1_mg/kg/day
B	B	79.380	10	3--1.0_mg/kg/day
	C	39.167	12	4--3.0_mg/kg/day
	C	38.458	12	5-10.0_mg/kg/day

1 ARGUS DEVELOPMENTAL NEURO PNDS PUP THYROID HORMONES - ALL VARIABLES

9

PROC GLM - MAIN EFFECT OF TRT - WITH TUKEYS

14:03

Tuesday, September 22, 1998

General Linear Models Procedure

Dependent Variable: T4

Pr > F	Source	DF	Sum of Squares	Mean Square	F Value
0.0001	Model	4	7.54525428	1.88631357	21.44
	Error	57	5.01410056	0.08796668	
	Corrected Total	61	12.55935484		
T4 Mean		R-Square	C.V.	Root MSE	
3.03677419		0.600768	9.766672	0.29659177	

Pr > F	Source	DF	Type I SS	Mean Square	F Value
0.0001	TRT	4	7.54525428	1.88631357	21.44

Pr > F	Source	DF	Type III SS	Mean Square	F Value
0.0001	TRT	4	7.54525428	1.88631357	21.44

1 ARGUS DEVELOPMENTAL NEURO PNDS PUP THYROID HORMONES - ALL VARIABLES
 10 PROC GLM - MAIN EFFECT OF TRT - WITH TUKEYS 14:03

Tuesday, September 22, 1998

General Linear Models Procedure

Tukey's Studentized Range (HSD) Test for variable: T4

NOTE: This test controls the type I experimentwise error rate, but generally has a higher type II error rate than REGWQ.

Alpha= 0.05 df= 57 MSE= 0.087967
 Critical Value of Studentized Range= 3.984
 Minimum Significant Difference= 0.3378
 WARNING: Cell sizes are not equal.
 Harmonic Mean of cell sizes= 12.23268

Means with the same letter are not significantly different.

Tukey Grouping	Mean	N	TRT
A	3.4093	15	1-----CONTROL
A	3.3182	11	2--0.1_mg/kg/day
A	3.1369	13	3--1.0_mg/kg/day
B	2.6800	11	4--3.0_mg/kg/day
B	2.5317	12	5-10.0_mg/kg/day